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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/078,247 | 02/14/2002 | Paul A. Wender | 8400-0013 | 3262 |

23980 7590 08/19/2008

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
5 Palo Alto Square - 6th Floor
3000 El Camino Real
PALO ALTO, CA 94306-2155

| EXAMINER | |
|---|---|
| GUDIBANDE, SATYANARAYAN R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1654 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/19/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/078,247 | WENDER ET AL. | |
| | Examiner | Art Unit | |
| | SATYANARAYANA R. GUDIBANDE | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,8-26 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *3,5,6,9,10 and 12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 8, 11 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/19/08 has been entered.

### *Election/Restrictions*

In the office action dated 11/26/07, the examiner withdrew the newly submitted claim 38 as being drawn to not further limit the invention recited in claim 1. Applicants argue that claim 38 recites that "the linker moiety comprises a half-life of between about 10 minutes and about 24 h in water at 37 °C and at a pH of approximately 7.4. As these elements are not recited in Claim 1, they do in fact limit Claim 1 by reciting further claim limitations with respect thereto. Accordingly, the Applicants contend the withdrawal of Claim 38 by the Office is in error, and the Applicants respectfully request that this claim be rejoined".

Applicant's arguments filed on 5/19/08 have been considered and found to be persuasive and hence claim 38 will be examined on the merit.

Applicant's amendment to claims 1 and 11 in the response filed on 5/19/08 has been acknowledged.

Claim 11 as amended is not free of art. A rejection of claim 11 appears below on the prior art found during an updated search.

Claims 1-6, 8-26 and 30-38 are pending.

Claims 3, 5, 6, 9, 10 and 12-35 have been withdrawn from further consideration as being drawn to non-elected species.

Claims 36, 37 have been withdrawn from further consideration as being drawn to non-elected invention (please see office action dated 11/26/07).

Claim 7 and 27-29 have been canceled.

Claims 1, 2, 4, 8, 11 and 38 are examined on the merit.

Any objections and rejections made in our previous office action dated 11/26/07 and not specifically mentioned here are considered withdrawn.

***Maintained Rejections***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 8 remain rejected under 35 U.S.C. 102(b) as being anticipated by Lorenzen, et al., The Journal of Cell Biology, 1995, 131, 631-643 as stated in our office action dated 3/15/06 and as reiterated below.

Response to applicant's arguments appears at the end of the reiterated rejection.

In the instant application, applicants claim a composition comprising a biologically active compound and a transport moiety comprising a structure $(ZY)_nZ$ wherein Z is L-arginine or D-arginine and Y is independently an amino acid that does not comprise an amidino or guanidine moiety and 'n' is an integer from 2 to 10.

Lorenzen, et al., teaches splicing of non-catalytic domain of human T-cell protein tyrosine phosphatase to generate 45-kD ($p45^{TC}$) and 48-kD ($p48^{TC}$) segments targeting the two forms to two different subcellular compartments. The $p45^{TC}$ segment localizes in the nucleus the sequence RKRKR that precedes the splice junction function acts as a nuclear localization signal (abstract). The splicing of the segment comprising the nuclear localization signal (RKRKR) (wherein R is arginine and K is lysine) with the tyrosine phosphatase enzyme as the biologically active molecule meets the limitations of claims 1 and 2. In the absence of a proper definition for a 'linking moiety' in the claims, splicing of the two segments meets the limitations of claim 7.

***Response to Arguments***

Applicant's argue that "the specification of the present invention refers to "self-immolating" at para 0060:

> Such [self-immolating] linking moieties in a transport moiety-biologically active compound conjugate contain a nucleophile (e.g., oxygen, nitrogen, and sulfur) distal to the biologically active compound and a cleavable group (e.g. ester, carbonate, carbamate, and thiocarbamate) proximal to the biologically active compound. Intramolecular attack of the nucleophile on the cleavable group results in the scission of a covalent bond, thereby releasing the linking moiety from the biologically active compound.

Lorenzen did not disclose a self-immolating linker moiety as provided by claim 1. In fact, the protein of Lorenzen is intact in-vivo, as the p48Tc form of TCPTP was isolated from

human peripheral T cells as the full length protein, including the region that the Examiner alleges to contain a self-immolating linker moiety. See Lorenzen, page 631, column 1, lines 19-22.

If in fact the protein as represented in Figure 1 did contain a self-immolating linker moiety and transporter of claim 1, as asserted by the Office, the isolated protein of Figure 1 would not contain at least amino acid residues 377 and onward. The entire sequence of TCPTP, including residues R377, K378, R379, K380 and R381, was isolated, which indicates that the protein of Lorenzen did not contain a self-immolating linker moiety.

Consequently, the Applicants contend that Lorenzen does not teach all of the elements of the rejected claims, a self-immolating linker moiety linking the biologically active compound and the transport moiety. Therefore, because Lorenzen does not teach all the elements of the rejected claims it fails to anticipate the claimed invention, in view of which, the Applicants respectfully request that the rejection of independent Claim 1, and claims 2, 4, 8, and 38 dependent upon it, be withdrawn".

Applicant's arguments filed 5/19/08 have been fully considered but they are not persuasive.

Applicants argument that the "definition of self immolating linking moiety" as "self immolating linking moieties in a transport moiety-biologically active compound conjugate contain a nucleophile (e.g., oxygen, nitrogen, and sulfur) distal to the biologically active compound and a cleavable group (e.g. ester, carbonate, carbamate, and thiocarbamate) proximal to the biologically active compound. Intramolecular attack of the nucleophile on the cleavable group results in the scission of a covalent bond, thereby releasing the linking moiety from the biologically active compound" is not recited in claim 1 as presented. Claim 1 as presented recite "a self-immolating linker moiety". The claim as recited does not indicate neither the

"nature of the linking moiety" in terms of "structural features" associated with it nor the "nature of the association (for e.g., covalent, ionic or hydrophobic)" of the linking moiety to biologically active compound and the transport moiety. By referring to the section that provides a generic definition of the linking moiety, applicants appear to import critical limitations into the claims. See MPEP 2111.01 "Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment."

Applicant's further argument that the figure 1 of the cited reference of Lorenzen did not disclose a self-immolating linker moiety as recited in claim 1 is also not persuasive. The argument was well addressed in the office action dated 5/19/08 and has been reiterated below.

"The schematic diagram depicts the catalytic region in black (biologically active moiety of the instant invention) coupled to the intron region represented by diagonal lines (linker of the instant application) to the non-catalytic region represented by the open area that contains the RKRKR moiety which is a part of nuclear localization signal (transport moiety)".

As mentioned above in the absence of a proper definition for the linking moiety in claim 1 as recited, the intron region of the figure 1 of cited reference of Lorenzen meets the limitation of the instant claim 1.

Hence the rejection of claims 1, 2 and 8 are proper and is maintained.

Claims 1 and 4 remain rejected under 35 U.S.C. 102(b) as being anticipated by Olsson, et al., Biochimica et Biophysica Acta, 1991, 1097, 37-44 as stated in the office action dated 9/21/06 and as reiterated below.

Response to applicant's argument appear at the end of the reiterated rejection.

In the instant application, applicants claim composition comprising a biological active compound and a transport moiety wherein the transport moiety comprises a structure $(ZY)_mZ$ wherein Z is L- or D- arginine and Y is independently selected from an amino acid that does not comprise an amidino or guanidino group.

Olsson, et al., discloses the peptide RSRSRSRSRSR, which can be represented as $(RS)_4R$ wherein 'R' is arginine and 'S' is serine. Olsson, et al., studied the association of chondroitin-6-sulfate proteoglycan with low-density lipoprotein (LDL) that is responsible for LDL accumulation during atherogenesis (abstract). Study indicated that RSRSRSRSRSR was most effective in blocking LDL-chondroitin-6-phospahte association. The peptide in association with chondroitin-6-sulfate meets the limitation of claims 1and 4 which is drawn to a composition comprising of biologically active compound and a transport moiety, wherein the transport moiety comprises a structure consisting of $(ZY)_mZ$ wherein Z is L- or D- arginine and Y is independently selected from an amino acid that does not comprise an amidino or guanidino group. The biologically active molecule in the reference is chondroitin-6-sulfate.

***Response to Arguments***

Applicants argue that the rejection as Olsson does not disclose a composition of claim 1, which contains a self-immolating linker moiety. A "self immolating linker moiety" as provided

in claim 1 and discussed above, is covalently bonded to the biologically active compound and the transport moiety. The complex of peptide RSRSRSRSRSR and chondroitin-6-sulfate of Olsson was not **covalently bonded** (emphasis added by the office).

Applicant's arguments filed 5/19/08 have been fully considered but they are not persuasive. Because, the claim 1, as presented (in the currently amended form) **does not** recite that the self-immolating linker moiety is **covalently bonded** to the biologically active compound and the transport moiety. On the contrary, the claim as recited does not indicate neither the "nature of the linking moiety" in terms of "structural features" associated with it nor the "nature of the association (for e.g., covalent, ionic or hydrophobic)" of the linking moiety to biologically active compound and the transport moiety.

Hence the rejection of claims 1 and 4 is proper and is maintained.

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, and 8 remain rejected under 35 U.S.C. 102(e) as being anticipated by US 7,070,807 B2 issued to Mixson as stated in the office action dated 9/21/06.

In the instant application, applicants claim composition comprising a biological active compound and a transport moiety wherein the transport moiety comprises a structure $(ZY)_mZ$

wherein Z is L- or D- arginine and Y is independently selected from an amino acid that does not comprise an amidino or guanidino group.

Mixson, discloses transport sequence $(RH)_4RG(RH)_4R$ (SEQ ID No. 13 in column 35) wherein 'R' is arginine and 'H' is histidine, that meets the limitation of claims 2 and 4. It is also disclosed that the arginine-histidine copolymer (Seq ID No. 13) was significantly better at enhancing transfection efficiency (column 24, lines 47-50). The reference also discloses that the transport moiety is inclusive of linear and branched polymers (page 8, lines 30-32). The reference discloses that the pharmaceutical component (biologically active compound of the instant application) interacts with the transport polymer (transport moiety of the instant application) by non-covalent or covalent interactions (column 15, lines 30-44) meeting the limitations of claim 1. In a specific example, Mixson studied a polymer:liposome:DNA complex for the transport efficiency of transport moiety (columns 23 and 24). The liposome was used as a linker, linking the transport moiety and the biologically active molecule DNA. They found that the transport polymer mixed with the DNA and then mixed with the liposome yielded the best transport efficiency and the efficiency was significantly better with use of Seq ID No. 13 a copolymer of arginine and histidine as mentioned earlier. This meets the limitation of claim 7, which requires the transport moiety attached to the biologically active molecule by a linking moiety to form a conjugate. Amino acids arginine, histidine and glycine shown in Seq ID No. 13 are gene encoded amino acids and hence meets the limitations of claim 8.

***Response to Arguments***

Applicants argue that, "Mixson disclosed an arginine-histidine copolymer (SEQ ID 13). Mixson disclosed that the transport polymer and the pharmaceutical agent may be covalently bonded. See Mixson, col. 15, lines 32-34. However, the only covalent attachments disclosed in Mixson were:

Such covalent attachment may be direct, for example through a -COOH group(s) of the polymer with an $-NH_2$ or-OH group of the pharmaceutical agent or the reverse. Alternatively the pharmaceutical agent may be attached to the transport polymer using a coupling agent such as di-carbodiimide [sic]. See Mixson, col. 15, lines 35-40.

If the covalent attachment was "direct" as defined by Mixson, the only residue which was directly attached to the pharmaceutical agent was arginine. The side chain of arginine does not have a nucleophile as discussed above for a "self- immolating linking moiety" as it has a guanidinium group, not an amine. The pKa of the guanidinium group of arginine is 12.48. Under in-vivo or in-vitro conditions capable of sustaining live cells, the guanidinium group is protonated and is not a nucleophile, and hence is not a self-immolating linker moiety as provided by claim 1.

Alternatively, if the covalent attachment is not direct, the only coupling agent which was disclosed by Mixson was carbodiimide. Thus the only possible intramolecular cleavage possible was via nucleophilic attack of the side chain guanidinium group of arginine. As discussed above, the guanidinium group in the side chain of arginine is not a nucleophile at physiologically relevant pH, and therefore the guanidinium group cannot comprise a self-immolating linker moiety for indirect covalent attachment as disclosed by Mixson".

Applicant's arguments filed 5/19/08 have been fully considered but they are not persuasive. Applicants argument that the $(RH)_4RG(RH)_4R$ (SEQ ID No. 13) in the cited reference is acting as the linking moiety is misplaced. In the rejection it is clearly stated that "In a specific example, Mixson studied a polymer:liposome:DNA complex for the transport efficiency of transport moiety (columns 23 and 24). The liposome was used as a linker, linking the transport moiety and the biologically active molecule DNA". In the example, the liposome and not the SEQ ID NO: 13 of the cited reference is the linking moiety. Hence the arguments of applicants with reference to guanidino group being protonated in *in vivo* conditions and being able to function as a nucleophile in the self-immolation of linking group is moot.

Hence the rejection of claims 1, 2, 4 and 8 is proper and is maintained.

***New grounds of rejections***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 recite a limitation that "linker moiety comprises a half-life in the range of between about 10 minutes and about 24 hours in water at 37 °C and at a pH of approximately 7.4". The pH of water is 7.0 and is neutral. The claims as recited requires that the pH to be 7.4

which is four-fold more basic (pH is expressed in the logarithmic scale) than the water. The water (solution) is basic only in the presence of added reagents such as basic ingredients such as alkaline reagents or it is a buffer comprising the buffer salts. It is unclear from the claim as recited claiming water to have pH of 7.4 in the absence of an alkali or buffer salt.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 8, 11 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant invention, applicants claim a composition comprising a biologically active compound, a transport moiety and a self-immolating linker moiety linking the biologically active compound and the transport moiety, wherein the transport moiety comprises a structure of $(ZY)_nZ$ wherein each Z is L-arginine or D-arginine, and each Y is independently an amino acid that does not comprise an amidino or guanidino moiety, and wherein n is an integer of from 2 to 10.

The claims as recited is for a **composition comprising** the a) biologically active compound, b) a transport moiety represented by formula $(ZY)_nZ$ wherein each Z is L-arginine or

D-arginine, and each Y is independently an amino acid that does not comprise an amidino or guanidino moiety, and wherein n is an integer of from 2 to 10 and c) self-immolating linker moiety. The claim as recited does not adequately define how the three components of the composition interact with other in the composition, i.e., whether the components a, b and c are covalently attached to each other, or the interaction between them is ionic, hydrophobic or hydrogen bond interaction. The claim as recited does not provide a partial or complete structural features of the composition where the biologically active compound is linked to the transport moiety by self-immolating linking moiety. The claim as recited provides a generic definition as "[s]elf- immolation moiety contains a nucleophile (e.g., oxygen, nitrogen and sulfur) distal to the biologically active compound and a cleavable group (e.g., ester, carbonate, carbamate and thiocarbamate) proximal to the biologically active compound. Intramolecular attack of the nucleophile on the cleavable group results in the scission of a covalent bond, thereby releasing the linking moiety from the biologically active compound (page 11, lines 2-27)". The definition provided in the specification encompasses any and all known and unknown molecules that contains a 'nucleophile' and a 'cleavable group' as recited. The specification provides three examples (structures 1-3) of the linking moieties on page 12 of the specification. The specification as disclosed does not adequately support the claims commensurate with the scope of the claim as recited. Lack of specific structure or structural formula for the composition comprising the afore-mentioned three components a, b and c and lack of specific structures or structural feature for the linking moiety leads to one of ordinary skill in the art to conclude that inventor had possession of invention at the time the invention was disclosed.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

The claim 1 as recited claims a composition comprising a biologically active molecule in general. The claim as recited not only does not provide a proper structural features for the composition comprising the three components a, b and c as afore-mentioned, it further claims any and all classes of biologically active compounds. The specific examples illustrate conjugation to acyclovir, hydrocartisone, taxol and retenoic acid. However, the biologically active compounds encompass class of compounds such as polypeptide, polynucleotides, polysaccharides, lipids, antibiotics, etc. The examples provided in the specification do not adequately support the claimed invention commensurate with the scope of the claim as recited.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

However, the cited prior art of Lorenzen discloses a TCPTP polypeptide domain that comprises of a catalytic region (biomolecule of the instant application), the intron or intervening sequence (the linker moiety of the instant application) and the basic cluster comprising RKRKR motif (the transport moiety of the instant application).

The cited reference of Mixson discloses a composition of polymer-Liposome-DNA wherein $(RH)_4RG(RH)_4R$ is the transport moiety, liposome is the linking moiety and DNA is the biologically active molecule.

Hence the claims as recited lack written description as the contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Reimekasten, 1998, J. Clin. Invest., 102, 754-763.

In the instant invention, applicants claim a composition comprising a biologically active compound, a transport moiety and a self-immolating linker moiety linking the biologically active compound and the transport moiety, wherein the transport moiety comprises a structure of $(ZY)_nZ$ wherein each Z is L-arginine or D-arginine, and each Y is independently an amino acid that does not comprise an amidino or guanidino moiety, and wherein n is an integer of from 2 to 10.

The reference of Reimekasten discloses that SmD183-119 peptide was coupled to KLH (Keyhole Lympet Hemocyanin) protein for immunization by disulfide linkage with the use of cystamine (page 756, column 1, paragraph 3). In the above conjugate, KLH protein corresponds to the biologically active compound of the instant invention, the peptide SmD1 83-119 that has the amino acid sequence VEPKVKSKKR EAVAG**RGRGRGRGRGRGRGRG**GGPRR corresponds to linker moiety (sequence underlined) and the transport moiety $(RG)_8R$ the portion of the sequence in bold letters. In this case arginine residue corresponds to 'Z' and glycine

residue corresponds to the 'Y' in $(ZY)_nZ$. The variable n=8 reads on the instant claims 1, 4 and 11. Also since 'Y' is glycine, it reads on instant claim 8. Since the transport moiety recites the amino acid glycine in the sequence, it reads on the currently amended claim 11. Also, since the peptide is coupled to the biologically active moiety KLH via disulfide linkage, it is labile and is a self-immolating linkage.

Therefore, the cited reference of Reimekasten anticipates instant invention.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Commonly assigned different inventive entities**

Claims 1 and 11 of instant application are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 of U.S. Patent No. 7,229,961 in view of Reimekasten, 1998, J. Clin. Invest., 102, 754-763. Although the conflicting

claims are not identical, they are not patentably distinct from each other because in the instant application, claims are drawn to a composition of comprising of genus of any and all known and unknown biologically active compounds, a self-immolating linker of unknown structural features and a transporter moiety (ZY)nZ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains. The claims of the cited U.S. Patent No. 7,229,961 ('961 patent)are drawn to a method comprising a conjugate comprising the any compound wherein the compound is attached to the delivery enhancing transporter through a linker of unknown structural features and the delivery enhancing transporter comprises of at least 5 guanidino or amidino moieties.

The '961 patent does not disclose the structural features of the transporter molecule as $(ZY)_nZ$ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains.

The cited reference of Reimekasten discloses the transport moiety as $(RG)_8R$ in the conjugate of KLH and SmD183-119.

Thus it would have been obvious to combine the teachings of '961 patent and Reimekasten to arrive at the instant invention. One would have been motivated to do so given the fact that Reimekasten had shown such a conjugate. Hence the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 11 of instant application are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11, 12, 14 and 15-17, of

U.S. Patent No. 6,593,292 in view of Reimekasten, 1998, J. Clin. Invest., 102, 754-763. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant application, claims are drawn to a composition of comprising of genus of any and all known and unknown biologically active compounds, a self-immolating linker of unknown structural features and a transporter moiety (ZY)nZ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains. The claims of the cited U.S. Patent No. 6,593,292 ('292 patent)are drawn to a method comprising a conjugate comprising the any compound wherein the compound is attached to the delivery enhancing transporter through a linker and the conjugate has the structural features shown in structures 3-6 in claim 1 and the delivery enhancing transporter comprises sufficient guanidino or amidino moieties.

The '292 patent does not disclose the structural features of the transporter molecule as $(ZY)_nZ$ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains.

The cited reference of Reimekasten discloses the instant transport moiety as $(RG)_8R$ in the conjugate of KLH and SmD1 83-119.

Thus it would have been obvious to combine the teachings of '292 patent and Reimekasten to arrive at the instant invention. One would have been motivated to do so given the fact that Reimekasten had shown such a conjugate. Hence the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 11 of instant application are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,730,293 in view of Reimekasten, 1998, J. Clin. Invest., 102, 754-763. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant application, claims are drawn to a composition of comprising of genus of any and all known and unknown biologically active compounds, a self-immolating linker of unknown structural features and a transporter moiety (ZY)nZ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains. The claims of the cited U.S. Patent No. 6,730,293 ('293 patent)are drawn to a conjugate comprising the compound selected from glucocorticoid, cyclosporin, FK506, etc., a delivery enhancing transporter comprising 5-25 arginine residues wherein the structural features of conjugate shown in structures 3-6 in claim 1.

The '293 patent does not disclose the structural features of the transporter molecule as $(ZY)_nZ$ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains.

The cited reference of Reimekasten discloses the instant transport moiety as $(RG)_8R$ in the conjugate of KLH and SmD1 83-119.

Thus it would have been obvious to combine the teachings of '293 patent and Reimekasten to arrive at the instant invention. One would have been motivated to do so given the fact that Reimekasten had shown such a conjugate. Hence the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 11 of instant application are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, and 17, 18, 20 and 21 of U.S. Patent No. 6,669,951 in view of Reimekasten, 1998, J. Clin. Invest., 102, 754-763. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant application, claims are drawn to a composition of comprising of genus of any and all known and unknown biologically active compounds, a self-immolating linker of unknown structural features and a transporter moiety (ZY)nZ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains. The claims of the cited U.S. Patent No. 6,669,951 ('951 patent) are drawn to a method of targeting a compound to a gastrointestinal epithelium wherein the conjugate comprising the compound and a delivery enhancing transporter comprising at least 5 guanidino or amidino moieties wherein the structural features of conjugate shown in structures 3-6 in claim 1.

The '951 patent does not disclose the structural features of the instant transporter molecule as $(ZY)_nZ$ wherein the Z is L or D-arginine and Y is any amino acids that does not comprise guanidino or amidino side chains.

The cited reference of Reimekasten discloses the transport moiety as $(RG)_8R$ in the conjugate of KLH and SmD1 83-119.

Thus it would have been obvious to combine the teachings of '951 patent and Reimekasten to arrive at the instant invention. One would have been motivated to do so given the fact that Reimekasten had shown such a conjugate. Hence the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US patents 6,593,292; 6,730,293; 6,669,951 and 7,229,961 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654